DOCKING STUDIES, SYNTHESIS AND EVALUATION OF ANTICANCER ACTIVITY OF CHALCONE BASED IMIDAZO-THIADIAZOLE DERIVATIVES

A Synopsis Submitted to Mandsaur University for Registration of Doctoral Programme

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Submitted by

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Abstract

Chalcones are naturally occurring pharmacologically active compounds which possesses variety of important biological activities. Heterocyclic derivatives of chalcone exhibits anticancer potential against numerous cancer cell lines through different mechanisms. Anticancer chalcone derivatives exhibits and improve the anticancer characteristics by adopting different approaches such as structural and functional manipulation along with substitution of aryl rings. Molecular hybridization and replacement in their structure with pharmacological important moieties has been useful for development of novel medicinal agent which shows significant anticancer properties with lesser toxicity. Evolution of new hybrid chalcone analogues occurred through the linkage between efficient chalcone with different adequate and prominent anticancer scaffold like thiadiazole, coumarine, benzothiazole and imidazole which have verified and proved inherent pharmacological role. However, chalcones performs a leading appearance in medicinal chemistry but utilization of their pharmacological potential still not enough. This project consists of attempt and generates the design with molecular docking studies followed by synthesizing growth of anticancer chalcone.

#

OUTLINE OF THE PROPOSED RESEARCH WORK

I. Title of the Research Work: "Docking studies, Synthesis and Evaluation of anticancer activity of Chalcone based Imidazo-Thiadiazole derivatives"

II. Importance/ Rationale of Proposed Investigation

As per current situation, cancer is one of the rapid growing and proliferative disease which is most critical related to other cellular disease. The well developed countries fulfilled with advance medical techniques also suffering from this disease which is having much more mortality rate. The condition is even worst in the non-developed countries for the reasons like lack of availability of quality drugs due to poorness and sometimes lack of knowledge.[1] Higher range of the cancers i.e 90–95% are caused due to behavioral factors and alternate lifestyle while 5–10% are inherited genetically. Numerous factors such as tobacco, diet, obesity, infections, ionizing and non-ionizing ultraviolet radiations, stress, lack of physical activity, and environmental pollutants which leads to cancers.[2] In tobacco smoke fifty known carcinogens are present, which containing polycyclic aromatic hydrocarbons and nitrosamines. In

worldwide one fifth cancer death are due to tobacco.[3] Diet, obesity and physical inactivity are other factors which leads to around 30–35% of cancer deaths. Approximately 14-20% of various cancer death is related to excess body weight in the United States. Physical inactivity affects the body weight and gives negative effects on endocrine and immune systems so it enhances cancer risk. Eating too much diet and Diets with lesser fruits, whole grains, and vegetables and also red meats are associated with various cancers.[4] In worldwide approximately 18% of cancer deaths are due to infectious diseases and it is different in region like 25% in Africa and 10% in developed world. Virus is one another major part for development of cancer various viruses such as human papillomavirus causes and develop cervical carcinoma, Epstein–Barr virus causes and develop B-cell lympho-proliferative disease and nasopharyngeal carcinoma. Hepatocellular carcinoma caused by hepatitis B and hepatitis C viruses and T-cell leukemia's caused by human T-cell leukemia virus-1.[2] Genetic mutation carriers are one another factor for cancer incidence and an inherited mutation in genes BRCA1 and BRCA2 which develops breast and ovarian cancer.[5]

Chronic myeloid or myelogenous leukemia (CML) is an uncommon cause of cancer-related mortality in the United States, with an estimated 8,430 new cases and 1,090 deaths anticipated in 2018.[6] CML is associated with the presence of the Philadelphia chromosome, a translocation between chromosomes 9 and 22 in humans, shows a fusion between the 5' end of the BCR gene and the 3' end of the ABL1 gene. In 1960 the Philadelphia chromosome was discovered, but the molecular genetic features were not understood until more recently. In the 1980s it was discovered that the Philadephia chromosome resulted in the BCR-ABL1 fusion gene.[7] In 2001, Imitinab comes over prior approval, CML was treated using interferon-alpha or bone marrow transplant. So, imatinib which is ABL1 kinase inhibitors have become the most common treatments for CML. Philadelphia chromosome should be found in other types of leukemias but presence of a BCR-ABL1 fusion gene is an absolute diagnostic method for CML, so it is present in all cases.

Chalcones are biosynthesized in a variety of plant species which are open-chain flavonoids.[8] Chemically, chalcones are 1,3-diphenyl-2-propen-1-ones, which consisting two aromatic rings connected through a three-carbon α,β-unsaturated carbonyl system.[8] Chalcone is an exceptional chemical origin having various biological activities, which covers anticancer,[9,10] anti-inflammatory,[11,12] antioxidant,[13] antimicrobial, anti-tubercular,[14] anti-HIV,[15] antimalarial,[16] and anti-

allergic activities.[17] Chalcones shows cytotoxic activities and having multiple mechanisms like cycle interruption, angiogenesis blockage, tubulin polymerization prevention and apoptosis induction.[20,21]

In addition, chalcone exhibits significant inhibition properties which protects and inhibits kinase, epidermal and vascular endothelial growth factor receptors. These EGFR and VEGFR required for tumor cell survival whereas cell proliferation accelerated due to kinase effect.[22-24] Furthermore, different reviews based on potent anticancer activities which has been exerted by chalcone analogues and its heterocyclic derivatives.[19,25-27] In last 7-8 years, the present perspective focuses on the medicinal chemistry techniques employed for the design and evolution of anticancer chalcones citing the examples reported in recent literature and patents (International, United States and Japanese patent databases) published.[18] The biological significance of these chalcone derivatives along with their therapeutic and practical potential against different types of cancer is also summarized herein

III. Scope of Proposed Investigation

One of the important and successfully applied technique for the design, and development of new and efficient chemotherapeutic agents is "Molecular hybridization."[25] It involves the combination of two definite pharmacophores or chemical moieties by linking and fusing each other to form novel hybrid molecule.[25,26] The selection of the chemical moieties is based on their known physical and chemical properties bio figures and it is expected that these hybrid molecules or moieties might exert synergistic or additive pharmacological activities.[27,28]

In this several structural modifications to the chalcone origin with conjugation of pharmacologically important heterocyclic ring or groups which are connected or replaced on either A or B phenyl ring have been shows that enhance their biological activity.

A novel series of imidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]prop-2-enoyl}-2*H*-chromen-2-one will be synthesized through Chaisen-Schmidth condensation. Newly synthesized products will be evaluated against particular cancer cell lines to analyze cytotoxic activity. These novel compounds should be effective by arresting G_0 or G_1 phase by exerting potent antiproliferative activities.[29]

IV Location:

a) Organization/Department where the work is to be done
    1. Mandsaur University, Mandsaur.
    2. B. R. Nahata College of Pharmacy, Mandsaur
b) Geographical Area of Investigation, if any
    1. In Madhya Pradesh, near to Ratlam.

V Research gaps identified in the proposed field of investigation:

A very successful implication of naturally occurring chalcones as probable anticancer agents has inspired numerous synthetic efforts to establish newer synthetic chalcones with anticancer properties.

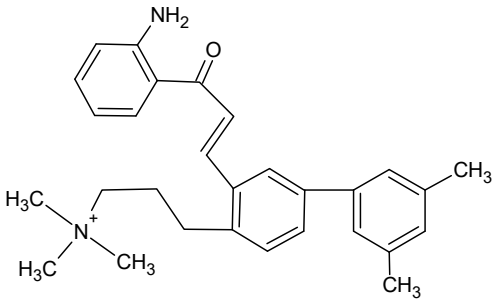
Development and improvement of anticancer properties of synthesized derivatives has been depends on rearrangement and manipulation of structural content. Two aryl rings of chalcone possesses significant role for promoting anticancer activities with the help of heterocyclic substitution with pharmacologically active moieties as well as through molecular hybridization. Diphenyl-2-propen-1-ones or chalcones having anticancer properties which is widely studied now days. So, Structural manipulations in diphenyl-2-propen-1-ones with fused imidazo-1,3,4-thiadiazole having electron donating and withdrawing substituents which will give positive reports on various cancer cell lines and molecular docking studies of synthesized derivatives with effective enzymes like Tyrosine kinase and cyclin dependent kinase will be carried out in this project.

VI Objective of the proposed study

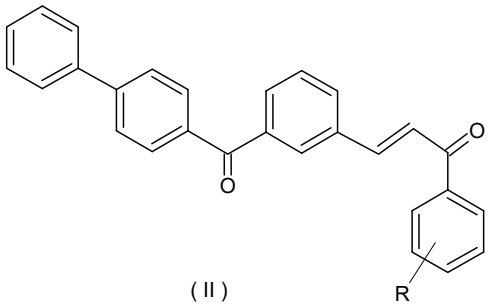
1. Some novel Chalcone based imidazo-thiadiazole derivatives.
2. To characterize the structure of the newly synthesized compound by different analytical techniques such as UV, IR, NMR and Mass spectral data.
3. Molecular docking studies of synthesized derivatives.
4. To evaluate the synthesized compounds for in-vitro anticancer activities.

VII Review of Work done on the Subject:

1. Dal. P. A. et al. have synthesized a series of substituted (E)-3-(4-phenyl benzoyl) chalcones (I, II) as potential anti bacterial agents.[30]

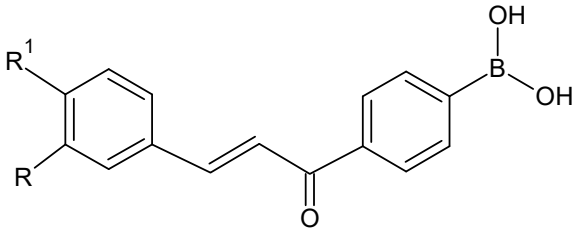


(I)



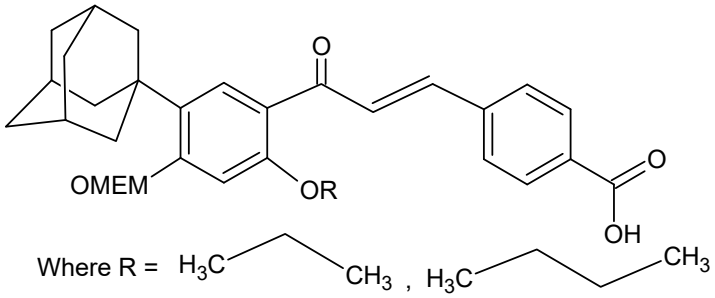
(II)

2. Srinivas K. Kumar *et al.* for a series of synthesized novel boronic-chalcone derivatives (III) followed by evaluation against breast cell lines for development of antitumor activity which shows boronic chalcones exerts toxic effects on breast cancer cells as related to different known chalcones.[31]



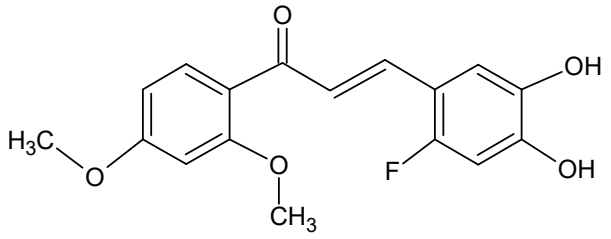
where R = I, Cl, F R^1 = H, Cl, Br (III)

3. Paula Lorenzo. *et al.* have been synthesized and reported a series of novel chalcones having adamantyl arotonoids (IV) which tested their IKB□□kinase β (IKKβ) activity exhibits inhibition property against cell growth as well as generates apoptosis in cancerious cells.[32]



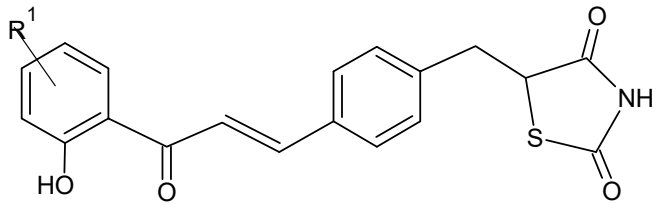
(IV)

4. Nakamura Chika et al. have been synthesized and reported fluorinated chalcones which analyzed and evaluated against different human cancer cells for antitumor activity. Synthesized compound (V) was reported as the most effective compound.[33]



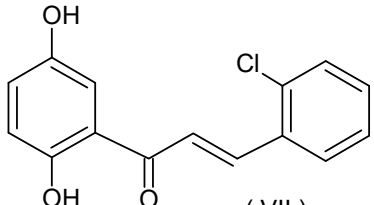
(V)

5. Jung et.al synthesized and reported novel series of 2’ hydroxy chalcone derivatives having thiazolodinone (VI) which has been evaluated for ligand binding activity with peroxisome proliferator activated receptor (PPAR). 2’-hydroxy-5’-methoxychalconylidene-thiazolidinone showed and appeared as a very potent ligand binding activity against peroxisome proliferator-activated receptor (PPAR) as compare to other synthesized derivatives of chalconylidene-thiazolidione.[34]



Where R^1=5'-OCH_3 (VI)

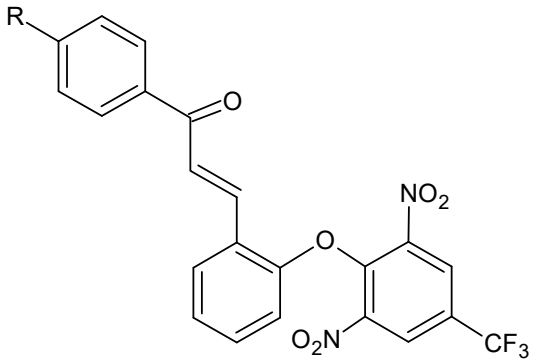
6. Nam Nguyen-Hai et al. have been synthesized and reported a new series of 2', 5'- dihydroxychalcones which analyzed and evaluated against HUVEC for cytotoxicity. Among the all compounds (VII) showed the highest activity on HCT116 cells.[35]



(VII)

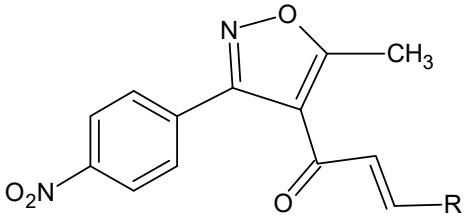
7. Hui Zhang et. al have synthesized and evaluate their potential inhibition and biological activities against tubulin. These synthesized compounds were assayed and analyzed against MCF-7 and A549 cell lines for in-vitro growth inhibitory action. Among the novel derivatives compound [VIII] represents most potent antiproliferative activity along with effective IC-50 values 0.03 to

0.95 µg/mL as well as higher rate of potent tubulin inhibitory activity with IC-50 of 1.42 µg/mL. Docking simulation also being performed to binding of compound to crystal structure of tubulin at colchicines binding site. This result determines the probable binding model of synthesized compound. These preliminary results shows that synthesized compound exhibits potent inhibitory action against the tumor cell growth which may be acts as a potent anticancer agent.[36]



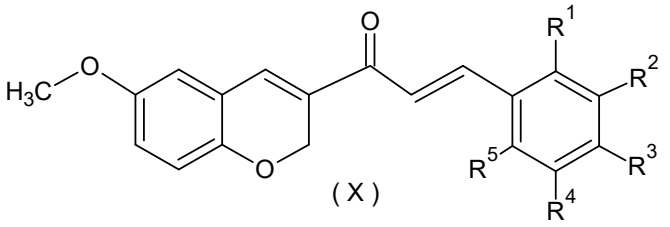
(VIII)

8. Wan et.al have been designed and synthesized new series of isoxazol aryl chalcone derivatives (IX) and evaluated against cancer cells lines for anticancer activity which determines that the synthesized compounds will affect human lung cancer cells by inhibiting proliferation.[37]



(IX)

9. Lim et al have been designed and synthesized methoxy chromenyl-chalcone derivative(X) which evaluated and tested against human cell lines for anticancer activity.[38]



(X)

VIII. Research methodology:

- **Hypotheses to be tested:**

Chronic myelogenous leukemia (CML) is a hematological stem cell disorder caused by liberated growth of myeloid cells in the bone marrow and the accumulation of excessive white blood cells. Abelson tyrosine kinase (Abl) is associated in in cell growth and proliferation.[39] A constitutively active tyrosine kinase that causes uncontrolled cellular proliferation. Imatinib is an Abl inhibitor and is currently used as first line therapy.[40] However, during the long term treatment with imatinib a high percentage of clinical regression has been observed.[41] Out of these regressed patients has several point mutations in and around the ATP binding pocket of the ABL kinase domain in Bcr-Abel.[42] In order to address the resistance of mutated Bcr-Abl to imatinib, 2(nd) generation inhibitors like dasatinib, and nilotinib were developed and used for the treatment of CML patients who are resistant to imatinib.[40]

In recent studies, we have pointed out the various significance of 1,3,4-thiadiazole as a potential moiety for antitumor drug design and development against some cancer cell lines through the inhibition of diverse molecular targets, containing tyrosine kinase, histone deacetylase (HDAC), focal adhesion kinase (FAK), and tubulin polymerization.[43] Cyclin dependent kinases are lead molecules that control cell cycle progression from one phase to the other. Hence, mutational changes in these molecules lead to the purturbed cell cycle having to uncontrolled cellular proliferation or cell death. In humans, mutations in cyclin dependent kinase which is responsible for association with nearly 50% of cancers.[44] 1,3,4-thiadiazolines nucleus is a biologically active heterocyclic ring, which is associated with a wide range of pharmacological activities[45]

This supported us to undertake the present research work to try some of the novel chalcone based imidazo-thiadiazole derivatives synthesized in our laboratory to address the anticancer activity against various effective cell lines. Which will be characterized by different analytical techniques such as Melting points, TLC, IR, NMR and Mass spectral data. In-vitro anticancer activity will be performed by MTT test on respective cancer cell lines and perform molecular docking studies of synthesized derivatives with enzymes Tyrosine kinase and Cyclin dependent kinase. If the present work is encouraging, it is expected that more number of drugs are available for the treatment of patients which are affected by various cancers. The

success of these inhibitors may also have greater implication in other diseases driven by kinases

- **Sources of Information:**
  a) Chemical Abstracts
  b) Indian Journal of Chemistry
  c) Indian Journal of Heterocyclic Chemistry
  d) Journal of Medicinal Chemistry
  e) Journal of Heterocyclic Chemistry
  f) European Journal of Medicinal Chemistry
  g) Bioorganic and Medicinal Chemistry Letters
  h) Word wide web
  i) J-Gate@ Helinet etc

- **Tools and Techniques of Research:**

  Chemicals and other reagents required for synthesis will be procured from standard company sources. Compounds will be synthesized by using standard techniques. The reactions will be monitored by TLC, purification of the compound will be done by standard procedures like recrystallization.

- **Plan of Work**

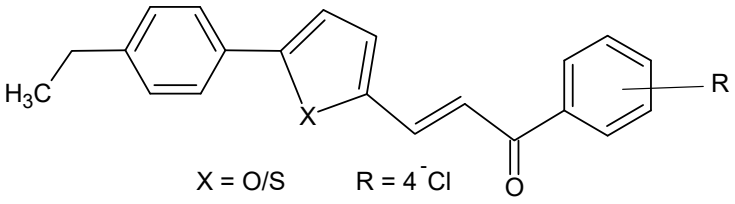
<u>Phase I</u>

1. **Raw material**

For synthesis of derivatives various chemicals will be purchased from sigma Aldrich, spectrochem pvt.ltd, and S.D. fine chem ltd. They were substituted carboxylic acid, ethanol, KOH, piperidine, substituted salisaldehyde, ethyl aceto acetate, DMF, POCl3, thiosemicarbazide, phenacyl bromide

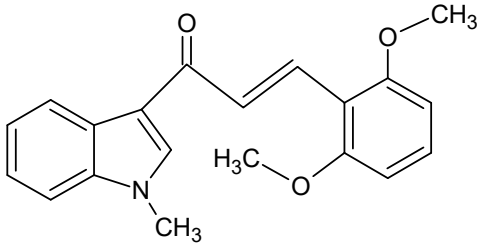
2. **Literature survey**

1) Solomon *et al.* compared the antiproliferative activity of aryl thiophenyl chalcones with aryl furanyl chalcones in breast cancer cells.[46]

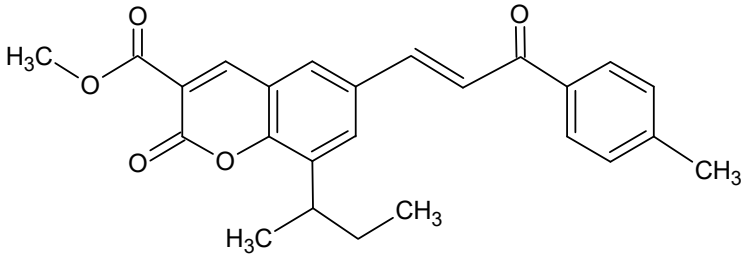


X = O/S R = 4 -Cl

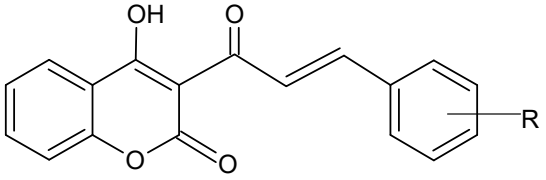
2) Martel-Frachet et.al. synthesized and evaluate a series of novel 1- (*N*-methylindolyl)-3 phenyl propenones against bladder carcinoma cells. Among the synthesized compounds methoxylated analogues which gives a very potent anticancer activity.[47]



3) Sashidhara *et al*. hav been designed and synthesized a new series of coumarin-chalcone hybrids which are evaluated against human cancer cells for in vitro cytotoxic activity. It is also analyzed and tested against normal fibroblasts (NIH3T3).[48]

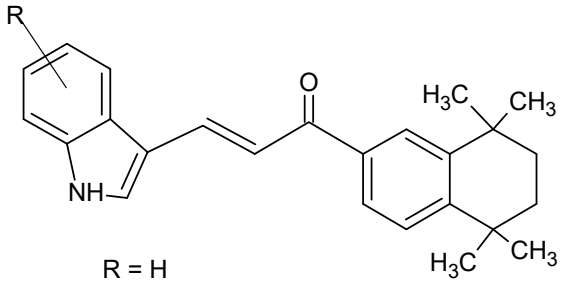


4) Patel et.al have synthesized a novel series of 4-hydroxy coumarinyl chalcones and evaluated against breast cancer cell lines for anticancer activity. Synthesized compounds have been evaluated against different breast cancer cell lines such as MCF7, MDAMB468, MDA-MB231 along with 184B5 which is non-cancerous breast epithelial cell line.[49]



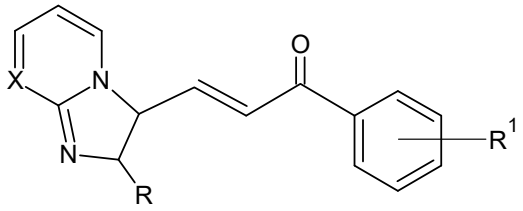
R = 2,3,4 -OCH_3

5) Gurkan-Alp et al. have been designed and synthesized a series of (E)-3-(5-substituted-1H-indol-3-yl)-1-(5,5,8,8- tetramethyl- 5,6,7,8-tetrahydro naphthalene-2-yl)prop-2-en-1-one derivatives which are evaluated agiant human breast, liver and colon cell lines for anticancer activity. The synthesized compounds possess indole and retinoid combination along with chalcone structural framework. Most of the novel indole retinoid compounds studied were found to possess the antiproliferative capacity in liver, breast and colon cancer cell lines.[50]



R = H

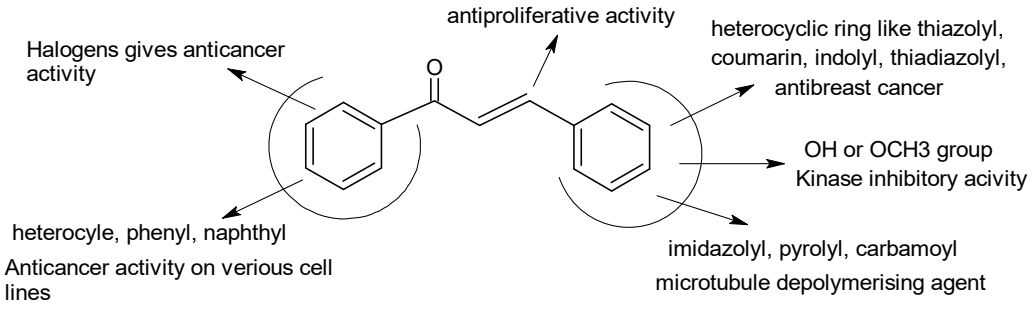
6) Karthikeyan et al. synthesized and evaluate isatin linked chalcones against breast cancer cell lines. The synthesized compound consist of chalcone and pharmacophoric elements of isatins which exerts good anticancer activity.[51]



R = CF_3 , R^1 = 3,4 di OMe & X=CH

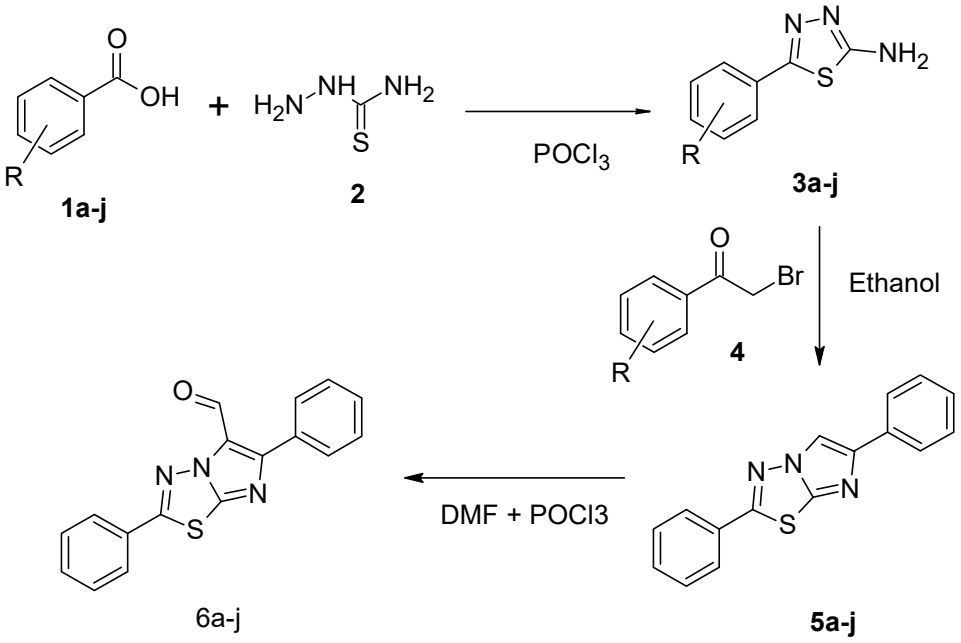
Phase II

1. **Material methods**
1. **Chemistry of chalcone:**



2. Scheme

SCHEME 1



3. Reaction mechanisms:

Step 1: Acylation with cyclization reaction

Several procedures were reported for the synthesis of 2-amino-1,3,4-thiadiazoles, in many of these methods the thiosemicarbazide was the starting material. Among the most important procedures was the one step acylation and cyclization reaction which was achieved by heating the carboxylic acid with thiosemicarbazide in the presence of phosphorus halide.

All forms of thiosemicarbazides are basis for synthesis of 1,3,4 Thiadizoles. 2-amino-1,3,4- thiadiazoles, intermediate for 1,3,4- thiadiazole derivatives, is prepared by cyclization of thiosemicarbazides or substituted thiosemicarbazides. represents thiadiazole formation by acylation/schiff base formation on Į-amino group initiates cyclization of thiosemicarbazides and on dehydrating agent (i.e) EDCI, DCC, TMSCl, TsCl, PPh3, SOCl2, PCl5, and diphenyl chlorophosphate.

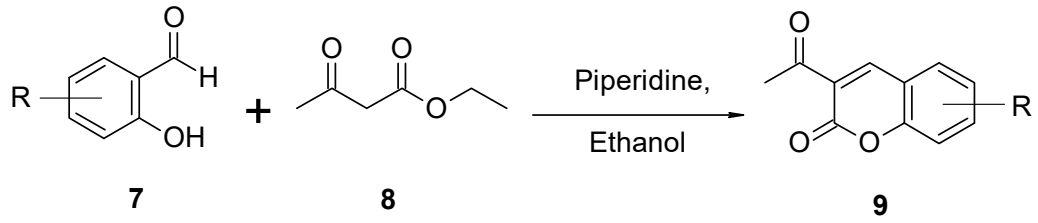
Step 2: Internal cyclization reaction[54]

N-4-Phenacyl 1,2,4-thiadiazolium salts, which are usually prepared by reacting phenacyl bromide with 5-Substituted 2-Amino-1,3,4-thiadiazole, undergo internal cyclization to give fused imidazole derivatives.

Step 3: Vilsmeier-haack reaction[55]

The vilsmeier-haack reaction of electron rich aromatic compounds, generally, afford aldehyde derivatives in good yeils. This reaction will carried out in presence of DMF and POCl3

SCHEME 2

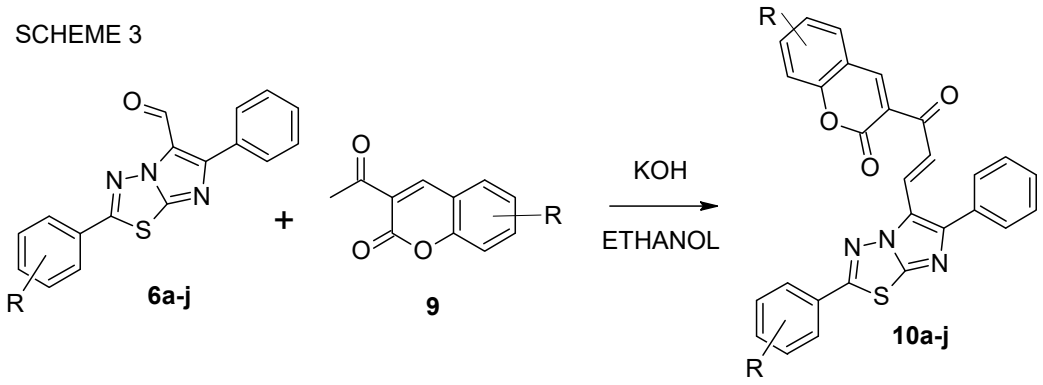


7 8 9

Step 4: base catalyzed condensation[53]

Base catalyzed condensation reaction between substituted salisaldehyde and ethyl aceto acetate to yield 3-acetyl coumarin

SCHEME 3



Step 5: Claisen-Schmidt reaction[56]

Substituted chalcone derivatives are generally carried out on basis of Claisen-Schmidt reaction using strong base such as NaOH or KOH in polar solvents like DMF or alcohol.

4. Chemicals and Instruments:

The required chemicals will be purchased from sigma Aldrich, spectrochem pvt.ltd, and S.D. fine chem ltd. etc. Melting points of synthesized derivatives will be determined in SHITAL digital programmable melting point apparatus. IR spectra will be record on Bruker spectrophotometer by using KBr pellets. The ^{1}H-NMR will be carried on Bruker Avance III NMR 300 MHz instruments using DMSO as solvent and TMS as internal standard.

Phase III

1. **Characterization**

a) Product Analysis and Evaluation

Synthesized series of novel derivatives will be analyzed by melting point, chemical test and TLC also evaluated under IR, NMR, Mass spectrometric analysis.

b) Synthesized product interpretation

Synthesized derivatives will be interpret with various spectrometric instruments.

c) Molecular docking studies:

In this study, Protein Data Bank (PDB) and National centre for Biotechnology Information (NCBI) will be used as chemical sources. The software will be used for experiment that, ACD/Chemsketch Ultra 10.0 for draw series of imidazo-thiadiazole Chalcone derivatives structures and Autodock 4.0, Discovery studio or autodock 4.0 for docking studies.

d) Anticancer activity [57]

Anticancer activity will be carried out on different cancer cell lines by MTT Assay.

MTT Assay: This is colorimetric assay that measures the reduction of yellow 3-(4,5-dimethythiazol- 2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The MTT enters the cells and passes into the mitochondria where it is reduced to an insoluble, coloured (dark purple) formazan product. The cells are then solubilized with an organic solvent (eg. DMSO, Isopropanol) and the released, solubilized formazan reagent is measured spectrophotometrically. Since reduction of MTT can only occur in metabolically active cells the level of activity is a measure of the viability of the cells

Phase IV

1. **Compilation and Conclusion**

According to exist literature and predicted analysis of the results from the our research of the docking, analytical, synthetical and computational study will be indicated that the designed novel Chalcone thiadiazolyl based –derivative should potent activation effect on CDK and tyrosine kinase receptor as potential anticancer target as well as treatment of a number of life threading disease.

However, further studies, like synthesis, *in-vivo* evaluation and mechanism of action of the derivatives will necessary to support this hypothesis. In future, The titled derivatives emerged as a lead for tyrosine kinase and CDK drug screening and research work on ADME/T (Absorption, Distribution, Metabolism, Excretion/Toxicity) properties of these derivatives can be tested in wet lab and research can proceed for clinical trials

IX. Expected outcome of research

cancer is a burgeoning major public health issue worldwide and economic burden as well as a threat to society which is increasing the risk of human affliction. So, we have to decide work on this disease which will be helpful for our society and peoples affected by various cancers who are economically poor to overcome this situation.

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